REMARKS

I. Preliminary Remarks

A Notice of Draftsperson Review was mailed with the Office Action, which indicated the drawings did not comply with 37 C.F.R. § 1.84(h)(2). The substitute figures submitted herewith comply with the rules set out in 37 C.F.R. § 1.84 and are identical to the originally filed figures. As the numbering of the figures was changed by the foregoing amendment, the references to the figures at pages 33 and 34 have been amended to reflect these changes. These amendments do not add new matter to the application.

The foregoing amendments to the claims are supported in the specification and do not add new matter to the specification. Amended claims 53 and new claim 79 are directed to methods that use a recombinant polypeptides having the amino acid of SEQ ID NO: 2 or a fragment thereof expressed by a host cell. These recitations were presented in original claims 54 and 56. New claim 80 is directed to methods that use a purified and isolated polypeptide as presented in original claim 55. In addition, claims 53, 55 and 81 are directed to polypeptides that are 95% identical to a fragment of SEQ ID NO: 2, which are supported at page 42, line 29 through page 43, line 2. New claims 79 and 80 are directed to polypeptides encoded by a nucleotide sequence that hybridizes under stringent conditions to the complement of SEQ ID NO: 1. These hybridization conditions are supported at page 44, lines 8-11. New claim 81 is directed to methods for assaying hu-Asp1 α-secretase activity comprising contacting a hu-Asp1 polypeptide of SEQ ID NO: 2 or a fragment thereof with a human APP isoform containing carboxy di-lysine. The polypeptide of SEQ ID NO: 2 was presented in original claim 56, while the human APP isoform containing carboxy di-lysine was presented in original claim 65. The remaining amendments were grammatical or corrected dependencies. Claims 1-52 were canceled without prejudice as being directed to unelected inventions.

II. The rejection under 35 U.S.C. § 112, second paragraph should be withdrawn.

In paragraph 7 of the Action, the Examiner rejected claim 64 under 35 U.S.C. § 112, second paragraph for improper antecedent basis. In particular, claim 64 recited "wherein the detectable label," and was dependent upon claim 53 which did not recite a detectable label. Claim 64 has been amended to depend from claim 63, which recites "wherein the APP substrate comprises a detectable label." In light of the foregoing

amendment, which corrects an obvious typographical error, the Applicants request the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

III. The rejection under 35 U.S.C. § 102(b) should be withdrawn.

In paragraph 9 of the Action, the Examiner rejected claims 53-64, 66, 67 and 78 under 35 U.S.C. § 102(b) as allegedly being anticipated by Bodovitz *et al.*, *J. Neurochemistry* 64(1): 307-315, 1995 (denoted herein as Bodovitz *et al.*). The Examiner stated Bodovitz *et al.* teaches an α-secretase assay comprising the steps of contacting HEK293 cells with APP, and therefore anticipates the methods of the present invention. The Examiner acknowledges that Bodovitz *et al.* does not teach the hu-Asp1 enzyme expressed in HEK293 cells; however as HEK293 cells are human cells they were considered by the Examiner to produce hu-Asp1.

To anticipate a claim, the prior art reference must set forth each and every element in the claim. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Circ. 1987). Amended claim 53 and new claim 79 are directed to methods of assaying α-secretase activity comprising a step of contacting an APP substrate with a recombinant hu-Asp1 polypeptide expressed by a host cell transformed or transfected with a nucleic acid molecule that encodes the polypeptide of SEQ ID NO: 2 or an active fragment thereof. Bodovitz *et al.* fails to teach or suggest use of a recombinent hu-Asp1 polypeptide of SEQ ID NO: 2, or any other particular recombinant protease, to measure α-secretase activity. The assays taught in Bodovitz *et al.* depend on the endogenous enzymatic activity of HEK293 cells and do teach any enzyme that cleaves APP to produce APPsol. Bodovitz *et al.* fails to teach the nucleic acid molecule, the recombinant host cell, or the recombinant polypeptide expressed by the cell, and therefore cannot be said to anticipate the claims.

Amended claim 55 and new claim 80 are directed to methods of assaying α-secretase activity comprising a step of contacting an APP substrate with a hu-Asp1 polypeptide that was purified and isolated. The features of a purified and isolated hu-Aps1 enzyme are not disclosed or suggested by the teachings of Bodovitz *et al.* As stated above, the assays taught in Bodovitz *et al.* use the endogenous enzymatic activity of HEK293 cells and do not use an enzyme that is purified and isolated. Bodovitz *et al.* fails to identify the enzyme or suggest how to purify and isolate it.

The Examiner also asserted that even though claims 54-55 and 60-61 recite process limitations, *i.e.* hu-Asp1 produced by recombinant methods, the novelty of the process lies in the product and not the steps used to produce it. While it may be appropriate in some circumstances to apply this type of logic to a product-by-process claim, it is inappropriate to apply this reasoning to a process claim. All of the limitations of the process, including the limitation that requires a recombinant production process to produce the enzyme, must be considered when assessing the novelty of the process claimed. The Applicants traverse the statement that the endogenous enzymatic activity referred to in Bodovitz *et al.* sufficiently meets the limitations of producing a recombinant hu-Asp1 polypeptide. Bodovitz *et al.* do not teach a nucleic acid sequence that can be used in the recombinant methods to produce the hu-Asp1 polypeptide of SEQ ID NO: 2. The endogenous enzyme may be purified and isolated from HEK293 cells but the teachings in Bodovitz *et al.* do not teach a particular enzyme to purify from HEK293 cells, nor provide any guidance on how to isolate and purify the enzyme. In addition, Bodovitz *et al.* refers to APP processing in HEK293 cells as "an unknown C-terminal cleavage event in the putative transmembrane domain of APP" (see page 307. col. 2) and contemplates the existence of more than one α-secretase enzyme (see page 313, col. 1). It would not be possible for one of skill in the art to use recombinant methods to produce hu-Asp1 or to purify and isolate hu-Asp1 using the teachings in Bodovitz *et al.*

In light of the foregoing amendment and remarks, amended claims 53-64, 66, 67 and 78 and new claims 79 and 80 are not anticipated by Bodovitz *et al.* Therefore, the Applicants respectfully request the rejection under 35 U.S.C. § 102(b) be withdrawn.

IV. The rejection under 35 U.S.C. § 103 should be withdrawn.

In paragraph 11 of the Action, the Examiner rejected claim 65 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bodovitz *et al.* in combination with Chyung *et al., J. Cell Biol.* 138(3): 671-80 and Marx *et al., Experimental Gerontol.* 34(6): 783-795. As described above, Bodovitz *et al.* allegedly teaches an assay for measuring α-secretase activity. The Examiner further asserts that Chyung *et al.* and Marx *et al.* each teach the advantages of the di-lysine modification in analysis of APP cleavage. In light of the foregoing amendment, claim 53-64, 66, 67 and 78-80 are either directed to a recombinant polypeptide of SEQ ID NO: 2 or an active fragment thereof or an isolated and purified

polypeptide of SEQ ID NO: 2 or an active fragment thereof, thus these claims are not anticipated by Bodovitz *et al.* for the reasons set out above. Therefore, the combination of Bodovitz *et al.* with Chyung *et al.*, and Marx *et al.* does not render claim 65 or any claim it depends from obvious.

New claim 81 is not restricted to methods that use recombinant or purified and isolated polypeptides, however, this claim should not be properly rejected under 35 U.S.C. § 103 as the combination of Bodovitz *et al.* with Chyung *et al.*, and Marx *et al.* does not render claim 81 obvious.

The teachings of Chyung *et al.* demonstrate that cleavage of APP to produce APPβ continued and was not affected by the presence of modified APP containing carboxy di-lysines. The specification demonstrates APP cleavage is increased by the presence of the carboxy di-lysines on APP, which is not suggested in Chyung *et al.* In addition, the effect of α-secretase cleavage on modified APP was not tested or suggested in Chyung *et al.* Further, Chyung *et al.* demonstrates that α-secretase processing of APP does not occur in an intracellular compartment, such as the endoplasmic reticulum; but occurs at or near the plasma membrane (see pg. 674 col. 1). Therefore, it was unexpected that modified APP with carboxy di-lysines would be useful in assays measuring α-secretase activity. There is no motivation for one of skill in the art to combine the α-secretase activity assays described in Bodovitz *et al.* with the teachings in Chyung *et al.* describing β-secretase cleavage of APP modified to contain carboxy di-lysines.

The teachings in Marx *et al.*, provide B-cell models useful for studying APP processing using known technology for retaining APP in the endoplasmic reticulum. These studies suggest that APP retained in the endoplasmic reticulum resulted in decreased production of sAPP and p3, which are produced by α-secretase cleavage of APP (see page 788). Therefore, there is no motivation for one of skill in the art to combine the α-secretase activity assays described in Bodovitz *et al.* with the teachings in Marx *et al.*, as these studies teach away from using APP containing di-lysines in assays to measure α-secretase activity.

For these reasons, Bodovitz *et al.* in combination with Chyung *et al.* and Marx *et al.* does not render claim 62 or new claim 81 obvious, and the rejection under 35 U.S.C. § 103 should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, pending claim 53-67 and 78-81 are believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

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Respectfully submitted,

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